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(54) Title: SMALL MOLECULES HAVING GLP-2 LIKE ACTIVITY

(57) Abstract

Described herein are non-peptide agonists of the GLP-2 receptor. In accordance with one aspect of the present invention there is provided, for use to treat subjects for which treatment with a GLP-2 peptide is indicated, a compound characterized as having a molecular weight of from about 100 Daltons to less than about 1,000 Daltons and which possesses GLP-2 receptor agonist activity.

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SMALL MOLECULES HAVING GLP-2 LIKE ACTIVITY

Field of the Invention

This invention relates to the use of small molecule agonists for the treatment of a condition for which a GLP-2 agonist is indicated.

Background of the Invention

GLP-2 (glucagon-like peptide-2) is a 33-residue peptide hormone which has a molecular weight over 3000 Daltons. It is a member of the glucagon family of peptides, and is produced by the endocrine cells of the intestinal epithelium. Whilst the sequence and structure of GLP-2 are homologous to those of glucagon and GLP-1, they are functionally distinct. The biological activity of GLP-2 is specific to the gastrointestinal (GI) tract.

For example, GLP-2 acts to stimulate the growth or regeneration of the lining of the small intestine, and may in fact function as the key regulator of intestinal epithelial growth. Increases in small intestine weight in GLP-2 treated animals are evident after just a few days of treatment (see WO96/32414). The exact mechanism by which GLP-2 stimulates proliferation of the intestinal epithelium, and thus restores a healthy epithelium after surgery or damage, for example, is currently unknown, although it has been shown to act through a GLP-2 receptor (see WO 98/25955).

Similarly, the exact mechanism by which GLP-2 inhibits apoptosis is currently unknown.

It has also been demonstrated that GLP-2 can proliferate the tissue of the large intestine (see CA 2,236,519). Further, GLP-2 can also proliferate the tissue of the upper GI tract, for example that of the esophagus and stomach (see WO98/25644).

Peptide analogs of GLP-2 have been shown to be even more potent than the natural peptide hormone. For example, a 33-residue peptide having minimal differences in sequence with respect to the natural peptide is approximately 3 times

as potent as the native peptide in a mouse model of intestinotrophic activity in the small intestine. This analog also demonstrates improved in vivo stability with respect to the natural peptide (see US 5,789,379).

Compounds which elicit a GLP-2-like response in vivo are attractive drug candidates, as they would have a role to play in a number of GI-related diseases or conditions, for example in the treatment of short-bowel syndrome, inflammatory bowel disease and rescue of the small intestine from the cytotoxic effects of chemo- or radiation-therapies (for example, NSAID-induced GI toxicity). Additionally, such compounds would be useful for the improvement of intestinal absorption following total parenteral nutrition (TPN).

Peptides, however, have a number of physical properties which make them difficult to formulate and use as therapeutic agents. For example, they have poor *in vivo* stability, bioavailability is low and they can be difficult to make and purify in the quantities necessary for a drug substance.

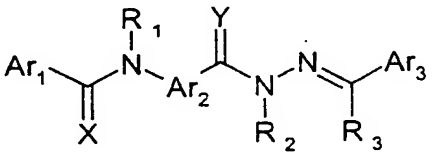
It would, therefore, be desirable to have access to drug candidates which possess the biological activity of GLP-2 *in vivo*, but which do not have the disadvantages noted above. For example, small molecules (that is, molecules with a molecular weight of less than about 1,000 Daltons and, more desirably, less than about 500 Daltons) which could be synthesised more routinely in the laboratory, and which could be tailored to have increased stability and bioavailability, as well as other desirable characteristics, would be attractive drug candidates. To date, however, no-one has demonstrated that such small molecules in fact are capable of activating a receptor that normally is activated, or "switched on", by a 33-amino acid peptide, which has a molecular weight over 3000 Daltons.

Summary of the Invention

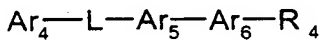
It has now been found that small molecules which are not peptides actually can activate the GLP-2 receptor. Thus, in accordance with one aspect of the present invention, there is provided, for use to treat subjects for which treatment with a GLP-

2 peptide is indicated, a compound characterized as having a molecular weight of from about 100 Daltons to less than about 1,000 Daltons, more preferably less than about 500 Daltons, and which possesses GLP-2 receptor agonist activity.

For example, compounds of Formula I or II, or a pharmaceutically acceptable salt, solvate or hydrate thereof, possess GLP-2-like activity and, thus, in accordance with embodiments of the present invention, are used in the treatment of GI-related diseases and conditions, such as those noted above, for which a GLP-2 receptor agonist is indicated.



Formula I



Formula II

where :-

Ar_1 to Ar_6 are independently selected aryl groups, wherein Ar is a 5- to 10-membered aromatic group which may contain up to two heteroatoms selected from the group consisting of O, S and N, and which is optionally substituted with up to 3 substituents selected from the group consisting of halo, hydroxy, lower alkyl, lower alkoxy and amino ;

X and Y are independently selected from the group consisting of O and S ;

R_1 and R_2 are independently selected from the group consisting of H, lower alkyl and optionally-substituted benzyl ;

R_3 is selected from the group consisting of H, lower alkyl and Ar ;

L is a C_1 to C_5 linear or branched alkylene group, which may be unsaturated ; and

R_4 is selected from the group consisting of H, lower alkyl and Ar.

Thus, it is an aspect of the present invention to provide a method for the treatment of a condition for which a GLP-2 agonist is indicated which comprises the administration of a compound of Formula I or Formula II to a subject in need of such treatment.

The invention also provides a method of proliferating the tissue of the upper GI tract in a subject in need thereof.

In another aspect of the invention there is provided a method of treating a subject having a damaged esophagus.

In another aspect of the invention there is provided a method of treating a subject having a damaged stomach.

The invention further provides a method of treatment of the aforementioned disorders in humans which comprises administering a composition comprising a therapeutically effective amount of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate or pro-drug thereof, and a physiologically-acceptable carrier.

Detailed Description and Preferred Embodiments

The present invention is based on the surprising discovery that activation of the GLP-2 receptor can be achieved using ligands that are remarkably smaller in size than the endogenous peptide ligand. It has been shown, for instance, that the endogenous GLP-2 receptor ligand, i.e. GLP-2 itself, is a 33-amino acid peptide that requires, for full agonist activity, at least the first 29 residues of the GLP-2 peptide (over 3,000 Daltons in size). Further C-terminal truncation leads to inactivation, and elimination of GLP-2 activity (see US 5,789,379). Moreover, it has also been shown that N-terminal truncation of GLP-2, by from 1-4 residues, leads to total elimination of GLP-2 activity (see WO98/03547). It has nevertheless now been shown, by the results herein presented, that much smaller molecules, less than about 1,000 Daltons in size, have structural properties sufficient to mimic the interaction necessary for GLP-2 receptor activation.

"GLP-2 receptor activation" is revealed as an increase of cyclic AMP (cAMP) resulting from incubation of a compound with a cell in which the GLP-2 receptor is coupled functionally to the adenylate cyclase signaling pathway. Cloning of the GLP-2 receptor, including the rat and human homologs thereof, and a description of assays suitable for determining GLP-2 receptor activation, are described in co-

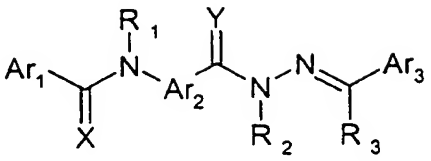
pending WO98/25955 published June 18, 1998, and by Monroe *et al.* in Proc. Natl. Acad. Sci., 1999 Feb 16; 96(4):1569, the entire disclosures of which are incorporated herein by reference. In general, the assays make use of mammalian cells, such as HEK 293 cells, that have been transfected by both (1) an expression cassette mediating production of the chosen GLP-2 receptor-encoding cDNA, and (2) a reporter gene construct in which a promoter responsive to cyclic AMP drives expression of a gene encoding a readily detectable reporter protein, such as luciferase. Compounds having GLP-2 receptor activation properties, referred to herein also as GLP-2 receptor agonists, are those compounds that, when incubated with such cells, elicit an increase in cyclic AMP production, as revealed by an increase in levels of the detectable reporter protein, relative to control cells lacking the GLP-2 receptor.

It is to be understood that the term "agonist" refers to a compound that elicits GLP-2 receptor activation either by direct binding to the GLP-2 receptor or through allosteric interaction therewith.

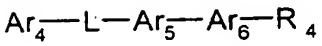
In another of its aspects, the present invention provides a method for identifying GLP-2 receptor agonists, in which the panel of compounds to be tested consists essentially of small molecule compounds rather than peptides, the compounds having a molecular weight of less than about 1,000 Daltons, and more preferably less than about 500 Daltons, the method comprising the steps of :

(1) obtaining, for use as a screening host, a cell useful for detecting GLP-2 receptor agonist activity;
(2) selecting, as a GLP-2 receptor agonist candidate, a compound having a molecular weight of less than 1,000 Daltons;
(3) incubating the selected candidate with the cell; and
(4) identifying, as a GLP-2 receptor agonist, a compound which elicits a GLP-2 receptor agonist response by said cell.

In embodiments of the present invention, the GLP-2 receptor agonists are compounds of Formula I or of Formula II :



Formula I



Formula II

where :-

Ar_1 to Ar_6 are independently selected aryl groups, wherein Ar is a 5- to 10-membered aromatic group which may contain up to two heteroatoms selected from the group consisting of O, S and N, and which is optionally substituted with up to 3 substituents selected from the group consisting of halo, hydroxy, lower alkyl, lower alkoxy and amino ;

X and Y are independently selected from the group consisting of O and S ;

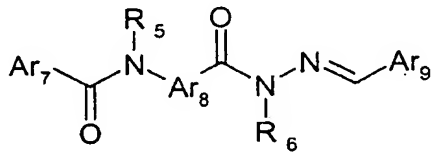
R_1 and R_2 are independently selected from the group consisting of H, lower alkyl and optionally-substituted benzyl ;

R_3 is selected from the group consisting of H, lower alkyl and Ar ;

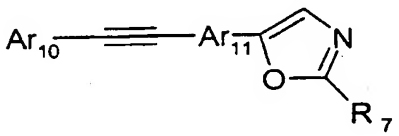
L is a C_1 to C_5 linear or branched alkylene group, which may be unsaturated ; and

R_4 is selected from the group consisting of H, lower alkyl and Ar.

Preferred embodiments of such compounds include compounds of Formula III or Formula IV :



Formula III



Formula IV

where :-

Ar_7 to Ar_{11} are independently-selected aryl groups, wherein Ar is as previously defined ;

R_5 and R_6 are independently selected from the group consisting of H, lower alkyl and benzyl ; and

R_7 is selected from the group consisting of H, Ar and lower alkyl.

In connection with the above Formulae, the following definitions apply:

The term "aryl" as used herein means a 5- to 10-membered aromatic group which may contain up to two heteroatoms selected from the group consisting of O, S and N, and includes phenyl, pyridyl, thiophenyl, oxazolyl, indolyl and the like.

The term "alkylene" as used herein means straight and branched chain alkylene radicals containing from one to five carbon atoms and includes methylene, ethylene and the like. Unsaturated alkylene groups include ethenylene, ethynylene and the like.

The term "lower alkyl" as used herein means straight and branched chain alkyl radicals containing from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, *t*-butyl and the like.

The term "lower alkoxy" as used herein means straight and branched chain alkoxy radicals containing from one to six carbon atoms and includes methoxy, ethoxy, propyloxy, isopropyloxy, *t*-butoxy and the like.

The term "halo" as used herein means a halogen atom such as fluoro, chloro, bromo and the like.

The term "amino" as used herein means an unsubstituted amino radical or a secondary or tertiary amino radical in which the substituents on the amine nitrogen are chosen from the group consisting of a lower alkyl group, a benzyl group, a benzoyl group and an acetyl group, any of which may be halo-substituted.

The term "pharmaceutically acceptable salt" means an addition salt which is compatible with the treatment of patients.

The term "solvate" means a compound of Formula I or Formula II, or a pharmaceutically acceptable salt of a compound of Formula I or Formula II, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable

solvent is physiologically tolerable at the dosage administered. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a hydrate.

The term "treat" or "treating" means to alleviate symptoms, eliminate the causation of the symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

The term "therapeutically effective amount" means an amount of the compound which is effective in treating the named disorder or condition.

The term "physiologically-acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient.

The definition of compounds of Formula I and Formula II includes within it scope prodrugs of the compounds of Formula I and Formula II. In general, such prodrugs will be functional derivatives of a compound of Formula I or Formula II which are readily convertible *in vivo* into the compound from which it is notionally derived. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs" ed. H. Bundgaard, Elsevier, 1985.

Compounds of Formula I and Formula II are useful as pharmaceuticals for the treatment of various conditions in which the use of a GLP-2 agonist is indicated, as outlined above.

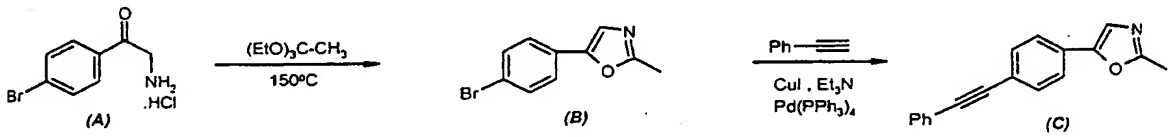
Illustrative compounds of Formula I and Formula II include :

2-Methyl-5-[(4-(phenyl ethynyl)]phenyl oxazole ;
2-Phenyl-5-[(4-(phenyl ethynyl)]phenyl oxazole ;
2-(Benzoylamino)-α-[(4-chlorobenzylidene) hydrazino]benzaldehyde ;
2-(Benzoylamino)-α-[(4-dimethylaminobenzylidene)hydrazino]benzaldehyde ; and

2-(4-Chloro-benzoylamino)-α-[((4-hydroxy-3-methoxy)benzylidene)hydrazino] benzaldehyde ;

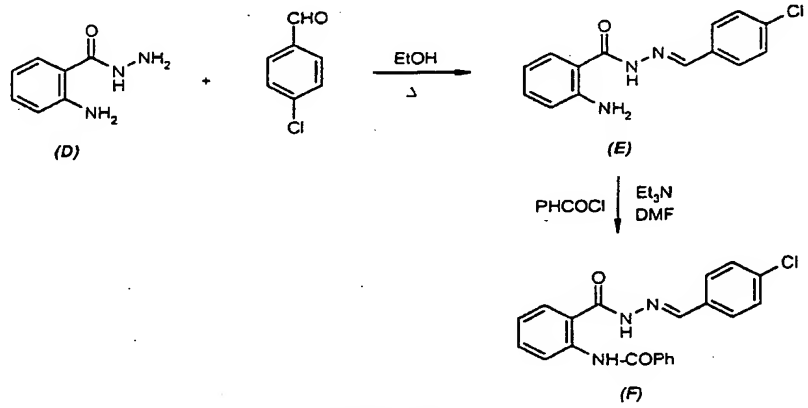
The compounds of Formula I and Formula II may be prepared by methods well known in the art.

For example, 2-Methyl-5-[(4-(phenylethynyl)]phenyl oxazole may be prepared as shown in Scheme 1, below. Treatment of α-Amino-4-bromoacetophenone (A) with triethyl orthoacetate gave oxazole (B). Coupling of this oxazole with phenylacetylene in the presence of copper iodide and tetrakis-triphenylphosphine palladium gave the product (C).



Scheme 1

In Scheme 2, below, treatment of hydrazine (D) with 4-Chlorobenzaldehyde gave hydrazone (E). Acylation of this hydrazone with benzoyl chloride gave product (F).



Scheme 2

Compounds of Formula I and Formula II function as agonists at the GLP-2 receptor, as demonstrated by the following assay. The GLP-2 receptor responds to GLP-2 and related agonists by increasing adenylate cyclase-mediated production of cAMP.

Test compounds were assayed for their ability to stimulate adenylate cyclase and increase cAMP. HEK-293 EBNA cells were stably transfected with the rat GLP-2 receptor and a luciferase reporter plasmid driven by the cAMP response element (CRE) driven by the thymidine kinase promoter (TK). Agonists of the receptor will therefore increase cAMP production, which will, in turn, stimulate synthesis of the luciferase enzyme.

For use in medicine, the compounds of the Formula I and Formula II can be administered in a standard pharmaceutical composition.

A pharmaceutical composition containing a compound of Formula I or Formula II may be adapted for oral, parenteral or rectal administration, and may be in the form of a tablet, capsule, powder, oral liquid, powder for reconstitution, injectable or infusible solution, suspension or suppository, as appropriate. A composition adapted for oral administration is preferred. More preferred are unit dose compositions in tablet or capsule form.

Compositions in tablet or capsule form may be in unit dose form, and may contain conventional excipients such as binders, fillers, lubricants or disintegrants. These can be manufactured by processes well known in the art, such as direct compression or wet granulation. Further, such tablets or capsules may be coated with, for example, an enteric coat which serves to resist disintegration in the stomach, or a coat which serves to otherwise prolong the duration of action of the active ingredient.

Oral liquid compositions may be in the form of a solution, suspension, emulsion or syrup, for example, or may be in the form of a product adapted for reconstitution using a suitable solvent (such as water) prior to use. Such preparations may contain additives such as suspending agents, emulsifiers, edible oils, preservatives, flavourings or colouring agents.

Parenteral compositions may be presented in unit dosage form, comprising a compound of the present invention, or pharmaceutically acceptable salt, solvate or pro-drug thereof, and a sterile vehicle. The compound may be dissolved or

suspended in the vehicle. Alternatively, the unit dosage form may take the form of a sterile powder which is to be reconstituted using a sterile vehicle prior to use. Such preparations may also contain additives such as antioxidants or stabilisers.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 1 to 25 mg) of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate or hydrate thereof. Compositions containing a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate or hydrate thereof , will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of from 1 mg to 500 mg, preferably between 10 mg and 400 mg, e.g., between 10 mg and 250 mg, or an intravenous, subcutaneous or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g., between 1 mg and 25 mg, of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, solvate or hydrate thereof, the compound being administered 1 to 4 times per day. Suitably, the compounds will be administered for a period of continuous therapy, for example for a week or more.

In accordance with the present invention, the small molecule GLP-2 receptor agonists herein described are usefully prescribed to treat the various medical conditions, diseases and disorders for which a GLP-2 receptor agonist is indicated. Among those medical conditions are those for which the GLP-2 peptide, or any active peptide analog thereof, are known to be useful. These conditions include a wide variety of gastrointestinal indications that are improved by the proliferative effects of the peptide on gastrointestinal tissue, as well as the protective and prophylactic effects of the peptide on such tissue. These effects can be utilized to advantage to treat conditions of various types of GI tissue, including small bowel, colon, stomach and esophagus.

In embodiments of the invention, the present compounds are used to enhance growth and/or function of gastrointestinal tissue in subjects, including poultry, livestock, and other animals including humans. The growth effects can be exploited particularly to treat subjects having resected gastrointestinal tissue as a result of surgical intervention, including those patients suffering from short bowel syndrome, The growth effects of the GLP-2 receptor agonist can also be exploited to rescue damaged gut

tissue, resulting for instance from inflammation including various sprues, ulceration, inflammatory bowel disease or Crohn's disease, or from infection or chemical insult, The present compounds can also be exploited to enhance gut function for instance to enhance the gut barrier function that is compromised in patients suffering from "leaky gut", and to treat subjects to enhance nutrient uptake, for instance, in those subjects that are challenged by chronic diarrhea, and other GI conditions associated with impaired nutrient absorption, such as inflammation of the bowel. The present compounds can also be used to modulate gut motility, and gastric emptying. The present compounds can also be used to prophylactically to protect the gut from chemical or other insult, for instance by administering the compound before treating the subject by radiation or chemotherapy.

Example 1 : 2-Methyl-5-[(4-(phenylethynyl)]phenyl oxazole ;

a) 5-(4'-bromophenyl)-2-methyloxazole

A mixture of 2-Aminomethyl-4'-bromophenylacetophenone (2.5g, 10mmol), p-toluenesulphonic acid monohydrate (50 mg) and ethyl orthoacetate (30mL) was heated, under Argon, at 160°C for 5 minutes, such that the ethanol that was formed during the reaction was distilled out. The resulting light brown solution was then refluxed under argon for 22 hours. Excess ethyl orthoacetate was removed under vacuum, with gentle warming, to leave a brown solid which was dissolved in ethyl acetate. The resulting solution was washed with saturated aqueous sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography on silica gel (1 : 1 ethyl acetate-hexanes as eluent). The title product was isolated as a pale yellow solid (1.94 g, 70% yield).

b) A mixture of 2-(4'-bromophenyl)-5-methyloxazole (1.2g, 4.37mmol), phenylacetylene (0.53mL, 1.1equivalents), tetrakis-triphenylphosphine palladium (252mg, 0.05equivalent) and triethylamine (15ml) was stirred under argon. Copper(I)iodide (250mg, 0.3 equivalents) was then added to this mixture. The resulting dark brown suspension was heated at 80°C, under argon, for 1 hour. More phenylacetylene (0.53mL, 1.1equivalents) was introduced and the mixture

heated for another hour. Excess amine was removed under reduced pressure. The resulting mixture was suspended in about 10mL of dichloromethane and filtered. Removal of the solvent under reduced pressure gave a crude product which was subjected to flash column chromatography on silica gel (40% ethyl acetate–hexanes eluent). The product isolated was found to contaminated with a small amount of coloured material. Thus, a second chromatography purification step was conducted using 20% ethyl acetate–benzene as the eluent. The desired product was obtained as a pale yellow solid (970 mg, 75 % yield). This material was further purified by recrystallization from hexanes/benzene to provide a crystalline white solid.

Example 2 : 2-(Benzoylamino)-α-[(4-chlorobenzylidene) hydrazino]-benzaldehyde

a) 4-Chlorobenzaldehyde, (2-Aminophenyl)hydrazide

A mixture of 2-aminophenylhydrazide (3g, 19.85mmol), 4-chlorobenzaldehyde (2.79g, 1equivalent) and ethanol (20mL) was refluxed for 3 hours under Argon. The reaction mixture was cooled to room temperature and seed crystals of the desired product introduced to induced crystallization. After standing at room temperature for 2 hours, the crystals were collected by suction filtration and dried under vacuum. The product was obtained as a pale yellow crystalline solid (1.33g, 25% yield).

b) To a cold (0°C) stirred solution of above compound (1.33g, 4.86mmol) and triethylamine (1.22mL, 1.8equivalents) in a mixture of dry dichloromethane (20mL) and dry DMF (3mL) under argon was added slowly benzoyl chloride (0.9mL, 1.6equivalents) over a period of one minute. The resultant suspension was stirred for 30 minutes at 0°C. The cooling bath was then removed and stirring continued for another hour. The mixture was concentrated under reduced pressure to a volume of about 6-7 ml. The thick slurry formed was diluted with 35mL of ethyl acetate and washed successively with 2 x 10mL portions of 1M hydrochloric acid and 2 x 10mL portions of brine. At this point the product started to slowly crystallize out of the solution. The resultant light suspension was slowly concentrated under reduced pressure to about half of the original volume and then allowed to stand at room temperature for 1 hour. Collection of the solid by suction filtration followed by drying under vacuum afforded the desired product as a crystalline white solid (820mg, 45%).

Example 3 : Determination of GLP-2 receptor agonists.

The GLP-2 receptor responds to GLP-2 and related peptide agonists by increasing adenylate cyclase-mediated production of cAMP. Test compounds were assayed for their ability to stimulate adenylate cyclase and increase cAMP. HEK-293 EBNA cells were stably transfected with the rat GLP-2 receptor and a luciferase gene controlled by the cAMP response element (CRE) driven by the thymidine kinase promoter (TK). Agonists of the receptor will therefore increase cAMP production, which will, in turn, stimulate synthesis of the luciferase enzyme.

Cells stably expressing the reporter (CRE-TK-Luc) and the receptor (rGLP-2R) were plated in 96-well plates in Dulbecco's Modified Eagle's Medium-Ham F12 Nutrient Mixture (DMEM-F12) containing 10% fetal bovine serum (FBS), and incubated at 37°C in a CO_2 incubator. The cells were allowed to grow to about 50% confluence before the assay (48-72 hr).

Culture media was removed from the plates, and test compound (10 μM) was added to each well in DMEM-F12/10% FBS, with a final concentration of 0.625% dimethyl sulphoxide. Positive control wells were treated with 20 nM GLP-2, and negative control wells were treated with media alone. Cells were incubated for 16 hr at 37°C in a CO_2 incubator.

Media was removed, and luciferase activity was assayed using the LucLite™ assay kit (Canberra Packard). Luminescence was measured on the TopCount microplate scintillation counter (Canberra Packard), and activity of each well was determined as 'counts per second' (cps). The activity in the wells for each compound was expressed as a percentage of the activity in the control (media alone) wells. An assay was deemed to be valid when the activity in the positive control wells was between 300% and 700% of the activity in the negative control wells.

Compounds which were active in the reporter assay were tested in a cell line transiently transfected with the CRE-TK Luc reporter, but without the rGLP-2

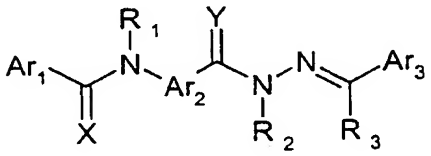
receptor. Specified compounds were not active in these cells, indicating that increases in cAMP accumulation are mediated solely by the GLP-2 receptor. In addition, dose response studies showed that compounds had maximum effect at 3 μM. Cytotoxicity was measured by LDH release using the Cytotox96™ cytotoxicity assay kit (Promega). None of the specified compounds is cytotoxic at concentrations up to 10 μM.

We claim :

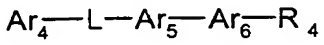
1. The use of a small molecule agonist of the GLP-2 receptor for the treatment of a condition for which a GLP-2 receptor agonist is indicated.

2. The use according to claim 1, wherein said agonist has a molecular weight of from about 100 Daltons to less than about 1,000 Daltons.

3. The use of a compound of Formula I or Formula II, or a salt, solvate or pro-drug thereof, for the treatment of a condition for which a GLP-2 receptor agonist is indicated:



Formula I



Formula II

where :-

Ar_1 to Ar_6 are independently selected aryl groups, wherein Ar is a 5- to 10-membered aromatic group which may contain up to two heteroatoms selected from the group consisting of O, S and N, and which is optionally substituted with up to 3 substituents selected from the group consisting of halo, hydroxy, lower alkyl, lower alkoxy and amino ;

X and Y are independently selected from the group consisting of O and S ;

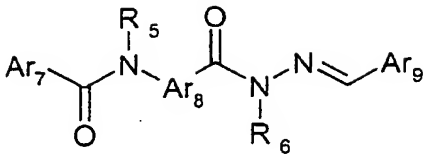
R_1 and R_2 are independently selected from the group consisting of H, lower alkyl and optionally-substituted benzyl ;

R_3 is selected from the group consisting of H, lower alkyl and Ar ;

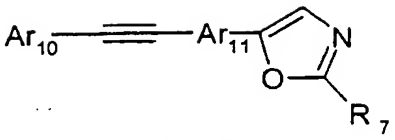
L is a C_1 to C_5 linear or branched alkylene group, which may be unsaturated ; and

R_4 is selected from the group consisting of H, lower alkyl and Ar.

4. The use of a compound of Formula III or Formula IV, or a salt, solvate or pro-dug thereof, for the treatment of a condition for which a GLP-2 receptor agonist is indicated.



Formula III



Formula IV

where :

Ar_7 to Ar_{11} are independently selected aryl groups, wherein Ar is a 5- to 10-membered aromatic group which may contain up to two heteroatoms selected from the group consisting of O, S and N, and which is optionally substituted with up to 3 substituents selected from the group consisting of halo, hydroxy, lower alkyl, lower alkoxy and amino ;

R_5 and R_6 are independently selected from the group consisting of H, lower alkyl and benzyl ; and

R_7 is selected from the group consisting of H, Ar and lower alkyl.

5. A method of treating a patient suffering from a condition for which a GLP-2 receptor agonist is indicated comprising the administration of a compound of Formula I or Formula II, or a salt, solvate or pro-dug thereof.

6. A method of proliferating the tissue of the upper GI tract in a subject in need thereof comprising the administration of a GLP-2 receptor agonist of Formula I or Formula II, or a salt, solvate or pro-dug thereof.

7. A method of treating a subject having a damaged esophagus comprising the administration of a GLP-2 receptor agonist of Formula I or Formula II, or a salt, solvate or pro-dug thereof.

8. A method of treating a subject having a damaged stomach comprising the administration of a GLP-2 receptor agonist of Formula I or Formula II, or a salt, solvate or pro-dug thereof.

9. The use of a compound having GLP-2 receptor agonist activity and a molecular weight of from about 100 Daltons to less than about 1,000 Daltons, to treat a subject that would benefit from enhanced gastrointestinal function.

10. The use according to claim 9, wherein the compound has a molecular weight of less than 500 Daltons.

11. The use according to claim 9, wherein the compound is of Formula I or Formula II as defined in claim 3.

12. The use according to claim 9, wherein the compound is of Formula III or Formula IV, as defined in claim 4.

13. The use according to claim 9, wherein the compound is selected from the group consisting of :

2-Methyl-5-[(4-(phenyl ethynyl)]phenyl oxazole ;

2-Phenyl-5-[(4-(phenyl ethynyl)]phenyl oxazole ;

2-(Benzoylamino)-α-[(4-chlorobenzylidene) hydrazino]benzaldehyde ;

2-(Benzoylamino)-α-[(4-dimethylaminobenzylidene)hydrazino]-benzaldehyde; and

2-(4-Chloro-benzoylamino)-α-[((4-hydroxy-3-methoxy)benzylidene)-hydrazino]benzaldehyde.

14. A method for identifying GLP-2 receptor agonists, the method comprising the steps of :

(1) obtaining, for use as a screening host, a cell useful for detecting GLP-2 receptor agonist activity;

(2) selecting, as a GLP-2 receptor agonist candidate, a compound having a molecular weight of less than 1,000 Daltons;

(3) incubating the selected candidate with the cell; and

(4) identifying, as a GLP-2 receptor agonist, a compound which elicits a GLP-2 receptor agonist response by said cell.

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Published:
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9 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/53208 A3

(54) Title: SMALL MOLECULES HAVING GLP-2 LIKE ACTIVITY

(57) Abstract: Described herein are non-peptide agonists of the GLP-2 receptor. In accordance with one aspect of the present invention there is provided, for use to treat subjects for which treatment with a GLP-2 peptide is indicated, a compound characterized as having a molecular weight of from about 100 Daltons to less than about 1,000 Daltons and which possesses GLP-2 receptor agonist activity. More particularly GLP-2 agonist used are small molecules containing hydrozine and aromatic group and the conditions to be treated are gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/CA 00/00245

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/15 A61K31/421 A61K31/167 A61P1/00
A61P1/04 G01N33/53 G01N33/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 52600 A (ONTARIO INC.) 26 November 1998 (1998-11-26) abstract page 2, line 16 - line 32 page 3 -page 5 page 10 -page 12	1,14
A	---	6-9
X	CA 2 236 519 A (ONTARIO INC) 2 November 1998 (1998-11-02) page 5 -page 7, line 11 abstract	1,14
A	---	6,9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2001	14/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/CA 00/00245

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MUNROE D G ET AL: "Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 FEB 16) 96 (4) 1569-73. , XP000960702 the whole document	14
A	SCOTT R B ET AL: "GLP-2 augments the adaptive response to massive intestinal resection in rat." AMERICAN JOURNAL OF PHYSIOLOGY, (1998 NOV) 275 (5 PT 1) G911-21. , XP000964807 the whole document	1,9
A	FR 2 168 136 A (FERLUI) 31 August 1973 (1973-08-31) the whole document	3

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 2,9,10,14 relate to a compound defined (inter alia) by reference to the following parameter(s): molecular weights (should between 100 and 100 Daltons).

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to perform a search only based on these parameters. Therefore a complete meaningful search on these claims is impossible.

Present claims 1,4,5 relate to an extremely large number of possible compounds/products (" a smalll molecule agonist of GLP-2 receptor") and methods ("a condition for which a GLP-2 receptor is indicated"). In fact, the claims contain so many options, variables or possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Moreover,present claims 3,11 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

For the same reason the term "prodrug" (claims 5-8) lack clarity and was NOT searched (no support nor specific exemple is given in the description).

Due to the above mentioned objections, the search has consequently been carried out for those parts of the claims which appear to be supported and disclosed, and for those parts of the application which do appear to be clear (and/or concise), namely on compounds of claim 4 (more particularly of claim 13), and on "conditions" mentioned in claims 6-9.

All claims were thus searched incompletely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No
PCT/CA 00/00245

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9852600 A	26-11-1998	US 6051557 A	18-04-2000
		AU 7516398 A	11-12-1998
		CN 1264307 T	23-08-2000
		EP 0981362 A	01-03-2000
CA 2236519 A	02-11-1998	NONE	
FR 2168136 A	31-08-1973	NONE	